

## Total Parenteral Nutrition— State of the Art

*These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Associate Professor of Medicine, and Robert C. Siegel, Associate Professor of Medicine and Orthopaedic Surgery, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.*

DR. SMITH:\* *I think that most people would agree that nutrition is one of the topics we neglect in most of our presentations. Today, Medical Grand Rounds will be devoted to an important topic in nutrition: hyperalimentation. Dr. Janet Abraham will present the case summary.*

### Case Summary

DR. ABRAHM:† The patient is a 24-year-old man with mixed embryonal testicular cancer in relapse with metastasis to retroperitoneal nodes, lung and liver, for which he had received several courses of chemotherapy before this admission.

On physical examination at this admission, blood pressure was 95/65 mm of mercury and pulse 82; these values changed to 90/60 mm of mercury with a pulse of 102 when the patient stood up. Weight was 81.6 pounds (37 kg). Findings on examination of head, eyes, ears, nose, throat, skin, lungs and heart were all unremarkable. On examination of the abdomen, the liver was found to be enlarged. Rectal examination showed a trace positive stool guaiac. Genitourinary examination showed the left testicle to be absent. Reflexes were 0 to 1+, symmetrical, and

no Babinski reflexes were present. The admission prothrombin time was 14.8 seconds. The patient was vomiting on admission and there was a question of a gastric outlet obstruction. It was felt necessary to give chemotherapy courses and to provide adequate nutrition. Therefore, hyperalimentation was begun. For the tumor, two courses of cyclophosphamide (Cytoxan®), adriamycin and cystplatinum were administered. This treatment resulted in a decrease in the size of the lung lesions and virtual resolution of the obstruction to gastric overflow.

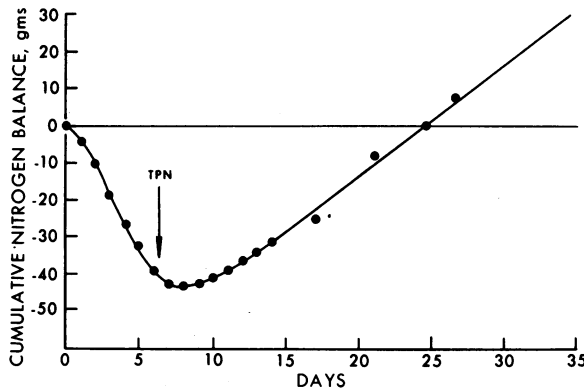
Administration was begun of a hyperalimentation solution (Travasol®) with 25 percent dextrose and appropriate concentrations of sodium, potassium, chloride, phosphate, magnesium and calcium. Folate was added biweekly; multivitamins and trace elements, including zinc, copper, cobalt, manganese and potassium iodine were administered daily. Topical safflower oil, which is 85 percent linoleic acid, was added during the sixth week because a greasy, brownish, scaling lesion of the eye margins, lids and nose developed, consistent with a deficiency of essential fatty acids or zinc. Zinc level at that time was 16 µg per ml (normal 55 to 150). The patient has gained 30 pounds while receiving hyperalimentation, dermatitis has resolved and hyperalimentation is now being decreased.

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# TOTAL PARENTERAL NUTRITION



**Figure 1.**—Nitrogen balance studies performed during total parenteral nutrition in a patient with regional enteritis. Administration of hypertonic dextrose and amino acids was associated with reversal of catabolism. TPN=Total parenteral nutrition.

DR. SMITH: *Thank you, Dr. Abrahm. We are extremely pleased to have Dr. George Sheldon to discuss this case and particularly to discuss the whole process of hyperalimentation and developments in the field.*

DR. SHELDON:\* Thank you, Dr. Smith. It is a pleasure to participate in Medical Grand Rounds. I had the opportunity to see this patient during his hospital stay. There were several things that should be commented on in his care. First, we usually provide vitamins and trace metals from the outset to prevent depletion. Also, we have a protocol for administering fat regularly so that the disorder seen in this patient, essential fatty acid deficiency, does not occur.

The capability of providing sufficient calories, protein, fat and other nutrients intravenously to maintain growth, development and weight has been a clinical reality for ten years. Total parenteral nutrition has evolved into a clinical subspecialty, as evidenced by the recent founding of a society (American Society for Parenteral and Enteral Nutrition [ASPEN]) and a journal (*J-PEN [Journal of Parenteral and Enteral Nutrition]*) which deals entirely with nutritional support. Moreover, recommendations are pending that would require hospitals using complex methods of nutritional support such as total parenteral nutrition to structure a team charged with its safe implementation.

Recent advances have occurred in many aspects of hyperalimentation.<sup>1-3</sup> Efforts to quantify accurately the nutritional status of patients and to

gauge the need and response to nutritional support have evolved. Bistrian and Blackburn have advocated use of a creatinine-height index, patterned after that of the World Health Organization. Published tables serve as standards for calculating the patient's ideal creatinine-height index and serve as an estimate of lean body mass. Since muscle mass is an important source of amino acids which can be recycled to support visceral proteins and maintain blood sugar through gluconeogenesis, a noninvasive nutritional assessment profile is a valuable clinical tool. Utilization of the World Health Organization standards for midarm muscle circumference is a simple assessment carried out with a tape measure, which provides an estimation of muscle protein status, also. A skin caliper can be used to measure the triceps skin fold; this provides an assessment of body fat composition.

Nitrogen balance is a time-honored measurement of the dynamics of nutritional depletion and repletion. Nitrogen balance reflects muscle degradation which through gluconeogenesis liberates nitrogen to be excreted primarily as urinary urea. A reasonable approximation of protein catabolism can be obtained by measuring daily levels of urea nitrogen in urine. When the excreted urea nitrogen is subtracted from the administered protein nitrogen, a reasonable approximation of balance is obtained (Figure 1).

Current investigations in our and other laboratories are focusing on the assessment of proteins of visceral origin, such as albumin and transferrin, and immunocompetence in addition to nitrogen balance.<sup>4,5</sup> "Visceral proteins" such as serum albumin are sensitive indicators of prolonged protein depletion. As the biological half-life of albumin is 20 days, a patient with hypoalbuminemia (less than 3.4 mg per 100 ml) obviously has significant protein depletion. Other "visceral proteins" such as those responsible for humoral immunity, erythropoietin and transferrin have significantly shorter half-lives than albumin. If hypoalbuminemia is present, the other "visceral proteins" are predictably more depleted. As malnourished patients usually die of sepsis and pneumonia, loss of muscle strength and diminished immunocompetence are perhaps more relevant assessment measures than nitrogen balance. Serum albumin, the weight-height index, transferrin levels, and urea balance should be followed in all patients in hospital with prolonged illness who are receiving nutritional support.

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TABLE 1.—*Indications for Nutritional Support*

- Anatomic or functional loss of gastrointestinal integrity
- Hypermetabolism
- Albumin less than 3.4 mg per 100 ml
- Prophylactic—"five-day rule" (see text)
- Multiple organ system failure: renal failure, hepatic failure, cardiorespiratory failure

In addition to laboratory tests, bedside assessment is essential. A recent operation, thermal injury or febrile illness will expend considerable calories and protein. In addition to the 1,800 calories needed for basic maintenance, 1°F of body temperature elevation will increase daily caloric expenditure by 500 to 700 kilocalories. Part of the bedside assessment is application of the so-called "five-day rule." If after five days of food deprivation it seems likely that oral feeding will occur within two additional days, no specific nutritional support is usually required. If the assessment is to the contrary, implementation of nutritional support by tube feeding, special diets or parenteral nutrition should be initiated to prevent further wasting of body cell mass (Table 1).

In addition to nutritional assessment, progress has occurred in access routes for parenteral feeding. Subclavian vein catheterization, popularized by Dudrick in 1967, remains the preferred route for administration of a hyperosmolar solution. However, subclavian vein thrombosis will occur in some patients in whom long-term intravenous feeding is required. Although single subclavian vein thrombosis is usually not a clinical problem, access for parenteral feeding is lost if it is bilateral. For that reason we frequently use a silastic catheter (Broviac catheter) which is inserted through a subcutaneous tunnel by way of the cephalic vein into the right atrium when prolonged intravenous feeding is anticipated. The Broviac catheter was developed for patients in whom home hyperalimentation is required and has been referred to as the "artificial gut."<sup>6</sup> This method of access is useful in patients who have lost much of the absorptive surface of the small intestine and is valuable in patients who have tracheostomy, because it allows the catheter exit site to be distant from the potential sepsis of the tracheostomy.

The capability for providing long-term total intravenous feeding out of the hospital was pioneered by Dr. Belding Scribner at the University of Washington. Unlike home hemodialysis for renal failure, many patients receiving home hyperalimentation are able to return to enteric feeding. Currently more than 150 patients in the

United States with anatomical or functional loss of gastrointestinal integrity are benefiting from this mode of therapy; our home hyperalimentation unit at San Francisco General Hospital is becoming increasingly busy.\*

### Starvation, Stress and Body Composition

Rational use of hyperalimentation requires knowledge of body composition. In an idealized 70 kg (154 pound) man, 15 percent of the body weight is in the form of protein, less than 2 percent of the body is in the form of glycogen, and the variable fat mass may range from 9 percent to 50 percent of total body composition. In the structure of these basic components are potential interconvertible energy sources. Maintenance of blood sugar levels occurs by catabolism of muscle and subsequent formation of glucose by the process of gluconeogenesis. During a period of brief starvation, 10 to 15 grams of nitrogen will be excreted in the urine daily, representing catabolism of protein to fulfill energy requirements.<sup>7</sup> After several days of food deprivation, lipolysis of fat begins to be a significant source of energy. Starvation adaptation, during which the body shifts from a protein source for energy to one of fat, is well established by two weeks of food deprivation. After 14 days of food deprivation, minimal amounts of nitrogen (<2.0 gms) are excreted daily and ketosis is present, indicating primary support of metabolic functions by fat. The shift from protein to fat as an energy source is associated with a reduction in urea synthesis and excretion, and in free water clearance. It is also associated with a low metabolic rate, decreased activity, and decreased serum insulin values. During starvation adaptation, the brain and heart utilize "ketone bodies" for energy substrate. Fat adaptation allows considerable time (over two months) to pass before death from starvation occurs.

In contrast to starvation, a patient with an illness characterized by increased catecholamine levels will have a high metabolic rate, a relatively fixed rate of muscle protein catabolism and will not adapt to the utilization of lipid substrates to provide energy needs. Such patients, whether their illnesses are medical, surgical or pediatric, can lose up to 30 percent of their lean body mass in one month if nutritional support is not provided. Although protein can be degraded

\*A home hyperalimentation registry has been established by the American College of Surgeons.

TABLE 2.—*Hypertonic Intravenous Nutrition, Requiring Central Venous Access*

Hyperalimentation meets requirements of
Calorie, protein, lipid
Electrolyte, vitamins, micronutrient
Calorie:nitrogen ratio—150:1
Hypertonic, hyperosmolar requiring central vein
Metabolic rather than gut substitute
Renal failure
Hepatic encephalopathy—special amino acid
Hypermetabolism—increased nutrients
Pediatrics—less glucose, more fat and amino acids

for the maintenance of important energy functions, body structure is lost when protein becomes the primary source of energy substrate. This is comparable to "burning the front porch to keep a fire going." The patient who is in addition deprived of food, although adapted to sparing of protein by fat, will continue to lose significant protein throughout the entire course of his or her period of nutritional deprivation.

In critically ill patients with multiple organ failure (renal failure, hepatic failure, respiratory failure), parenteral nutrition is begun as soon as the patient is hemodynamically stable. Aggressive nutritional support is an obligatory form of management to meet the increased substrate requirements and metabolic needs of catastrophically ill patients.

### Techniques of Intravenous Nutritional Support

Two basic methods for providing intravenous nutrition are currently popular and involve hypercaloric or hypocaloric regimens. Total parenteral nutrition (hyperalimentation) should meet the requirements for calories, protein, vitamins, electrolytes, minerals, macronutrients and fat (Table 2). As hyperalimentation is hypertonic and hyperosmolar, it requires a central venous access route into an area with rapid blood flow. It has a calorie-to-nitrogen ratio of approximately 150:1 and the calorie source is concentrated dextrose. Micronutrients, macronutrients and vitamins are provided to meet recommended daily requirements as well as special needs. The standard solutions assume adequate renal function to clear the free water and urea produced by the metabolism of these substances. Standard hyperalimentation basically serves as a gut substitute and requires adjustment based on nitrogen balance and the other assessment measures of efficacy.

For some patients the need for hypertonic intravenous feeding is a metabolic one rather

than substitution for inadequate gastrointestinal tract function. In patients with disorders of nitrogen metabolism such as renal or hepatic failure, individual determinations of calorie and protein needs are essential because of the inability of such patients to utilize nutrients appropriately or excrete end products of protein metabolism. In patients with acute renal failure who have high energy needs, insulin resistance and inability to clear free water with urea, the parenteral feeding has special objectives. Patients with renal failure require a very hypertonic solution with a calorie-nitrogen ratio in excess of 450:1, and only about a third of the usual provision of protein in the form of amino acids. The objective of the therapy is to provide the maximal amount of calories with the minimal quantity of free water and nitrogen. When this regimen is effectively administered, gluconeogenesis is inhibited and blood urea and serum potassium levels are lowered. One study found improved survival in patients with acute tubular necrosis receiving dextrose and amino acids as compared with patients receiving hypertonic dextrose alone.<sup>8</sup>

Recently, with Dr. Fischer of Massachusetts General Hospital, we have begun testing a special amino acid mixture for use in patients with hepatic encephalopathy.<sup>9</sup> Patients with hepatic encephalopathy have decreased serum levels of branched chain amino acids and increased levels of aromatic amino acids. Provision of standard hyperalimentation solutions as well as orally given protein exacerbates this disturbance, which can be correlated with degree of hepatic encephalopathy. The solution developed by Dr. Fischer brings the plasma amino acids to normal levels, presumably rectifies abnormal neurotransmission and has been associated with improvement in hepatic encephalopathy in a small group of patients awakening from coma.

Targeting of special amino acid solutions to defined metabolic problems or diseases is an area of investigation being pursued actively by industry. In addition to renal and hepatic failure, cardiac cachexia is associated with lowered left ventricular stroke volume and filling pressures, both of which can be improved by aggressive nutritional therapy.

Patients with thermal injury or severe trauma frequently have a 150 percent increase in basal metabolic expenditure (BME) paralleling their degree of catabolism. Extensive thermal injury is associated with 40 to 50 grams of nitrogen loss

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**TABLE 3.—Hypotonic Intravenous Nutrition,  
Administered Through Peripheral Vein**

"Protein Sparing" Therapy	
Isonitrogenous, hypocaloric	
Provides micronutrients and macronutrients and vitamins	
Amino acids alone	
Amino acids plus dextrose	
Amino acids plus lipid	
Indications	
Intermediate between normal and intravenous alimentation	
Morbid obesity	
Fatty liver—total parenteral nutrition	
Limitations	
Weight loss continues	
Blood urea nitrogen level rises	
Hypoglycemia	
Expense	
No substitute for total parental nutrition or tube feeding	

daily, a degree of protein breakdown which will be present until the burn is healed. Extensive injury may be associated with a loss of 30 percent of lean body mass in three to four weeks, unless aggressive nutritional intervention is employed.

Meeting nutritional needs by a hypocaloric isonitrogenous infusion which provides all nutrients except total calories is attractive because it can be administered through a peripheral vein (Table 3). Nitrogen balance can be improved by the peripheral infusion of amino acids in combination with intravenous fat.<sup>10,11</sup> Not only can nitrogen balance be improved by hypocaloric provision of amino acids, but albumin synthesis can be promoted by infusion of hypocaloric solutions.<sup>12</sup> The main problem with hypocaloric regimens is deciding when they should be used. Persons unfamiliar with hyperalimentation may, because of unfamiliarity with subclavian vein access routes, choose a hypocaloric routine for a patient who needs maximal nutritional support. Moreover, patients with brief illnesses or operations do not require any special nutritional support beyond the routine use of electrolytes and 5 percent dextrose solution.

Our current use of hypocaloric routines is confined to two groups of patients. The first group includes patients who are likely, but not certain, to resume oral nutrition within a week of food deprivation. Temporizing for a week with hypocaloric routines rather than initiating hypercaloric alimentation via the subclavian vein seems rational in such patients. Moreover, there are patients whose body decomposition is adequate but because of diagnostic tests and perhaps gastric

obstruction may require up to a week of preparation for a surgical procedure and will benefit by maintaining protein integrity while they lose weight. Patients in whom hepatic steatosis develops from the long-term provision of hypertonic solutions of dextrose and protein should be treated intermittently with dextrose-free amino acids. This reduction in the amount of dextrose received will reverse the structural hepatic changes.

### Solution Composition

The caloric base for parenteral nutrition is hypertonic dextrose. It is commercially available in concentrations of 70 percent, 50 percent or less. Hypertonic dextrose is added to a protein base to provide a usual infusion concentration of 25 to 30 percent dextrose. The maximal concentration which can be prepared, about 47 percent dextrose, is used in patients with large caloric requirements or when a high caloric density per unit volume is required such as in renal failure.

The other available caloric source is fat. A safe lipid emulsion (Intralipid®) containing the essential fatty acids in a soybean emulsion has been available for over one year. It is a 10 percent solution containing 1.1 calories per ml and is used twice a week to prevent essential fatty acid deficiency.

Many sources of protein are available. The whole proteins initially used, hydrolysates of casein or fibrin, are effective but are becoming less popular because of the quantity of nonutilizable nitrogen they contain. Synthetic amino acids are used frequently today because they meet recommended daily requirements for amino acids or the needs of special illnesses such as renal or hepatic failure. Until this past year only one amino acid solution (Freamine®) was on the market. At present, two additional amino acid solutions (Aminosyn®, Travamin®) have become available. There is little to choose among these products. Some solutions are premixed with electrolytes, which may limit flexibility in their use. Physicians must therefore be familiar with the products used in their hospitals.

Although electrolyte requirements must be individually tailored to each clinical situation, anabolism requires approximately 40 mEq of potassium and 20 mEq of phosphate for each 1,000 kilocalories infused (Table 4). Magnesium, sodium, trace metals such as copper, zinc, manganese and daily vitamin infusion are necessary also.<sup>13</sup> Vitamin K, folic acid, and vitamin B<sub>12</sub> are not con-

TABLE 4.—*Electrolyte Requirements*

Sodium	As needed
Potassium	40 mEq per 1,000 kilocalories
Phosphate	20 mEq per 1,000 kilocalories
Calcium	35 mEq per 1,000 kilocalories
Magnesium	8 mEq per 1,000 kilocalories

tained in commercial multivitamin preparations and need to be added weekly or biweekly.

### **Mechanical, Septic and Metabolic Complications**

Mechanical complications from placement of the subclavian catheter occur in less than 5 percent of patients.<sup>14</sup> Any structure, however, in the region of the subclavian vein (brachial plexus, lung, subclavian artery, thoracic duct) may be injured. The catheter may be inadvertently threaded into the jugular vein. Pneumothorax, however, remains the most common complication. Subclavian vein thrombosis secondary to prolonged administration of hypertonic solution is more common than thought. If subclavian vein thrombosis is bilateral, access for parenteral nutrition is difficult.

Sepsis is the most serious complication of hyperalimentation. Over the past five years, documented catheter sepsis rates have fallen from 30 percent to less than 3 percent in most units. *Staphylococcus epidermis* is the commonest organism associated with hyperalimentation catheter sepsis; candidiasis seldom occurs. Reduced rates of catheter sepsis are directly related to the formation of hyperalimentation teams, protocols and standardized practices. At San Francisco General Hospital, the sepsis rate between 1970 and 1972 was 28.6 percent. During the past year, the sepsis rate in more than 300 patients was less than 3 percent, with no patient requiring treatment of sepsis other than catheter removal.

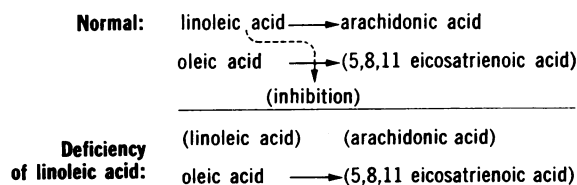
Metabolic complications of the infused hyperalimentation solution relate to the substrate infused and deficiencies which develop. Complications of hypertonic dextrose infusion may occur when greater than 0.5 gm of glucose per kg of body weight is administered per 24 hours, if the patient has insufficient insulin (diabetes mellitus) to metabolize the sugar, or if insulin resistance (burn, uremia, sepsis, injury) is present. Hyperosmolar, nonketotic dehydration may occur within 12 hours in susceptible patients and has a mortality rate greater than 40 percent. It is treated by administration of insulin, but is best avoided by

frequent analyses of urine and blood glucose. Many patients receiving parenteral nutrition will have blood glucose values of 175 to 200 mg per 100 ml. The addition of 10 to 15 units of regular insulin per each 1,000 dextrose calories is a useful practice. When a hyperalimentation solution is abruptly discontinued, hypoglycemia may occur. Gradual slowing of the infusion rate prevents this rebound hypoglycemia.

Metabolic complications secondary to the intermediary metabolism of protein are to some degree dependent on the product utilized. Fibrin hydrolysates have been associated with hyperammonemia. Hyperammonemia, however, can also occur when synthetic amino acids are administered, suggesting that higher concentrations of arginine than are currently present in commercially available solutions may be required. The first commercially available amino acid solution (Freamine) had the amino acids as chloride salts. With metabolism of these amino acid salts, hydrogen and chloride ions would be liberated with resultant metabolic acidosis. Current amino acid solutions are primarily acetate salts and seldom disturb acid base balance. Prerenal azotemia from infusion of protein solution may occur if the patient is dehydrated; if the calorie to nitrogen ratio is too low, or if the solution is administered too rapidly.

Essential fatty acid deficiency is frequently caused or exacerbated by hyperalimentation because intravenous dextrose infusions are associated with elevated serum insulin values and depressed lipolysis. Biochemical evidence of fatty acid deficiency may be detected within three days of initiating hyperalimentation. Fatty acid deficiency is diagnosed biochemically by an increase in the triene to tetraene ratio which is reflected as an elevation of 5,8,11 eicosatrienoic acid, a lipid which is usually undetectable in the serum (Figure 2). Essential fatty acids (linoleic acid, for example) are necessary for a variety of essential body functions, such as formation of prostaglandin-E, wound healing, immunocompetence and integrity of the skin. The clinical appearance of fatty acid deficiency is that of a flat, scaly dermatitis. Subcutaneous tissue structure is altered in advanced cases to give the axilla and groin a pachydermal appearance.

Hypophosphatemia is the most serious electrolyte abnormality associated with hyperalimentation.<sup>15</sup> It occurs within three days when phosphate-free hyperalimentation solutions are



**Figure 2.**—Essential fatty acid deficiency. Because the essential fatty acid, arachidonic acid (tetraene), is formed from the essential fatty acid, linoleic acid, inadequate linoleate results in the deficiency of both of these essential fatty acids. When linoleic acid levels are low, 5,8,11 eicosatrienoic acid (triene) is formed from oleic acid stores. Linoleic acid normally inhibits the formation of 5,8,11 eicosatrienoic acid (triene) from oleic acid. In the deficiency of linoleic acid, 5,8,11 eicosatrienoic acid is formed and detectable. The broken lines depict regulatory effects, and the parentheses denote absent to minimal concentrations.

administered. Hypophosphatemia is associated with decreased serum phosphate and increased tubular reabsorption of phosphate, reflecting an extracellular to intracellular shift of phosphate ion. Because inorganic phosphate is a cofactor in the Emden-Myerhof pathway of glucose metabolism, hypophosphatemia causes low red cell values of 2,3 diphosphoglycerate (2,3 DPG) and adenosine triphosphate (ATP). Low values of 2,3 DPG and ATP result in increased hemoglobin affinity for oxygen and, when very severe, in hemolytic anemia.<sup>16</sup> Patients with hypophosphatemia may have high cardiac output, tachypnea and convulsions.

Trace metal deficiencies associated with long-term parenteral nutrition are being recognized with increasing frequency.<sup>13</sup> Copper deficiency, clinically apparent by refractory anemia, is common. Zinc deficiency, with impaired wound healing, was uncommon when the fibrin hydrolysates were the usual protein base. The increased use of amino acid solutions, if trace elements are omitted, is associated with low zinc values. Magnesium, manganese, iodine, as well as chromates, all should be added to the infusion when prolonged parenteral nutrition is anticipated.

## Conclusion

Intravenous nutrition, called hyperalimentation by Dudrick and Wilmore<sup>17</sup> when first described, is among the most important advances in medical science of the past ten years. In addition to providing a simple method for nutritional support by a route other than the gastrointestinal tract, it has stimulated clinical and basic investigation in a neglected area of medicine, nutrition. Hyperalimentation, when provided by a team of health professionals (doctor, nurse, pharmacist, dietitian) can be safely administered for the benefit of patients treated by all disciplines of medicine.

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